DRAFT Medical Coverage Policy | Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases

EFFECTIVE DATE: 08|01|2023
POLICY LAST UPDATED: 04|26|2023

OVERVIEW

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloidblasts, primarily in the peripheral blood and bone marrow. The myelodysplastic syndromes (MDS) represent a spectrum of clonal bone marrow diseases, with heterogeneous presentations that typically include one or more cytopenias, defective differentiation of blood cell progenitors into mature functional cells, and an increased rate of progression to acute myeloid leukemia (AML). These secondary AML cases carry a worse prognosis than de novo AML cases. Furthermore, there are myeloid neoplasms that share overlapping characteristics with both MDS and myeloproliferative neoplasms (MPNs), such as chronic myelomonocytic leukemia (CMML). The World Health Organization (WHO), has designated these diseases separately as MDS/MPNs, distinct from either MDS or MPNs. The myeloproliferative neoplasms (MPNs) represent a group of rare clonal bone marrow diseases, have a median age at onset of 65-70 years, and heterogeneous presentations that typically include overgrowth of one or more of the myeloid cell lineages in the marrow, with increased circulation of mature forms in the peripheral blood, and an increased rate of progression to acute myeloid leukemia (AML). Symptomatology varies between the different diseases, typically related to the specific proliferating cell lineages.

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Acute Myelogenous Leukemia (AML)

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following clinical circumstances:

- Newly diagnosed patients with AML who are undergoing induction therapy, and who are suitable candidates for post-induction transplantation or consolidation therapy at the time of testing, and meet one of the following cytogenetic criteria:
  - normal karyotype
  - core binding factor
- Previously diagnosed patients with AML, who have not responded to induction chemotherapy, or who have progressed following induction. The patient must be a candidate for transplantation at the time of the testing.
- Patients with AML, who have responded to treatment, either chemotherapy or transplantation, with evidence of relapse.

Myelodysplastic Syndromes (MDS)

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following clinical circumstances:

- Patients with clinical signs or symptoms of myelodysplastic syndromes (MDS) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN), in whom clinical, laboratory, and pathologic assessment are nondiagnostic.
- Newly diagnosed MDS or MDS/MPN patients either
  - stratified by the International Prognostic Scoring System IPSS or Revised International Prognostic Scoring System (IPSS-R) as intermediate risk, or
  - in MDS with ringed sideroblasts/refractory anemia with ringed sideroblasts (RARS).

Limitations

- Repeat Genomic Sequential Analysis Panel testing is not reasonable and necessary in MDS after initial diagnosis and risk stratification.

Myeloproliferative Neoplasms (MPN)

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following circumstances:

- Diagnosis: Clinical signs or symptoms of myeloproliferative neoplasm (MPN) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN) when
  - clinical, laboratory, and pathologic assessment are nondiagnostic; and
  - CML excluded (BCR-ABL1 negative)
- Risk Stratification: Newly diagnosed primary myelofibrosis (PMF) not already classified as high-risk by Dynamic International Prognostic Scoring System (DIPSS) Plus
- Monitoring: Higher-risk MF (INT-1, INT-2, High-Risk) with progression on therapy

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online portal for participating providers.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Genomic sequence analysis panels in the treatment of hematolymphoid diseases may be considered medically necessary when the medical criteria above are met.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory benefits/coverage.

BACKGROUND

Acute Myelogenous Leukemia (AML)

The American Cancer Society estimates that approximately 60,000 new cases of leukemia will be diagnosed in 2016, with one-third classified as acute myelogenous leukemia (AML). It accounts for the most annual deaths from leukemia in the United States. The median age of diagnosis is 67, with 54%diagnosed at 65 years or older (and approximately one third diagnosed at 75 years of age or older). Moreover, AML lies at one end of a spectrum of neoplastic myeloid diseases that includes myelodysplastic syndromes (MDS), which often progress to AML, and which are even more common in patients of advanced age, with an incidence of approximately 1/5000 patients over the age of 70.

AML is an aggressive disease that requires immediate diagnosis and treatment, with an average 5 yr survival rate of 28%, depending on a number of clinical and biologic variables, including acquired genetic alterations within the leukemic cells. Early treatment of AML generally consists of high-dose cytotoxic chemotherapy to induce remission, followed by consolidation (i.e., post-remission) chemotherapy and/or bone marrow transplantation.

Steadily accumulating genomic evidence shows that certain acquired genetic alterations within the leukemic cells are strong predictors of prognosis in AML and, accordingly, are essential factors in the decision whether a patient should undergo bone marrow transplantation. These alterations have been set aside as determinants of independent diagnostic categories in WHO AML guidelines, and as essential for AML management in NCCN guidelines.

Importantly, the indication for molecular biomarkers in AML is somewhat different from other cancers, such as non-small cell lung cancer, in that the markers themselves are often not the direct targets of treatment. In

AML, these molecular genetic biomarkers are incorporated into a risk-based treatment stratification that determines whether or not to recommend transplantation.

Moreover, AML patients often have multiple combinations of these essential mutations, again in contrast to the mutually exclusive driver oncogene alterations seen in solid cancers such as non-small cell lung cancer. In AML, the clinical effect of driver mutations can be modified by the wider genomic milieu, either additively or interactively. Therefore, complete assessment of AML patients requires testing multiple biomarkers concurrently, rather than a sequential single-biomarker approach. In this regard, panel testing is becoming the preferred approach.

The spectrum of genetic abnormalities that are relevant in AML is broad, and includes specific sequence variants within genes, copy number changes, and structural variants such as chromosomal translocations. Smaller scale mutations require a molecular diagnostics method (e.g., sequencing) for analysis, while larger scale chromosomal abnormalities may be analyzed using either molecular diagnostics or cytogenetics (e.g., FISH, karyotype) methods. Molecular diagnostics and cytogenetic testing play a complementary role in helping refine prognosis, particularly in cytogenetically intermediate risk normal karyotype AML (NK-AML), or those with core binding factor where KIT mutations help refine the prognosis.

The following molecular genetic biomarkers are considered necessary for diagnosis and management of AML: CEBPA, FLT3, KIT, NPM1, TP53, RUNX1. These variants represent essential determinants of prognosis and therapy and are shown to lead to safe and effective therapy selection.

Myelodysplastic Syndromes (MDS)

According to the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, the overall incidence of MDS is approximately 5/100,000 per year, primarily in adults. MDS is rare in patients under the age of 40, but much more common in older patients, with incidence of 30/100,000 among ages 70-79, and 60/100,000 in patients 80 years and older.

MDS treatment can range from surveillance/observation to high dose chemotherapy and bone marrow transplantation, with the principal determining factors being the patient's overall health and co-morbidities, and prognostic categorization. MDS has historically been classified by a combination of traditional laboratory techniques, such as demonstration of stable cytopenias by complete blood count, microscopic examination of a bone marrow biopsy, and bone marrow cytogenetic studies. Other than the clinical feature of the number of cytopenias and specific cytogenetic changes found recurrently in MDS, all other diagnostic criteria in MDS rely upon light microscopy findings. These include the number of cell lineages (i.e.,platelets, red blood cells, white blood cells) affected by dysplasia, the percentage of immature "blast" cells, and the presence or absence of a characteristic pattern of iron deposition in immature red blood cells called ring sideroblasts. Low risk MDS is associated with dysplasia affecting only one cell lineage, with or without ring sideroblasts, and isolated large deletions involving chromosome 5 (5q-). High risk disease is associated with dysplasia across multiple lineages, increased blast percentages, and complex karyotype. With the exception of SF3B1 mutations, no specific mutations are incorporated into the current diagnostic criteria of MDS.

However, evidence has steadily accumulated over the first two decades of the 21st century showing that certain specific acquired genetic alterations within the myeloid cells are strong predictors of prognosis in MDS and, in the case of SF3B1, are necessary diagnostic markers as well. In addition, other somatic alterations may support the diagnosis of MDS in certain contexts. MDS can be challenging to diagnose, due to the subjective morphologic assessment of dysplasia, and a multitude of benign reactive conditions that can manifest as peripheral cytopenias and cytologic atypia that are especially prevalent in the elderly population. In this regard, the demonstration of these clonal molecular alterations in clinically and/or morphologically ambiguous cases can help establish a diagnosis of MDS and expedite therapy earlier in the disease course, before progression to a more overt, and life-threatening, condition. Accordingly, a number of specific genetic

alterations are included in the NCCN guideline recommendations as necessary for the diagnosis and management of patients with MDS.

Forty-seven different gene mutations have been identified as recurring findings in MDS, including TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1, EZH2, ZRSR2, STAG2, CBL, NRAS, JAK2, SETBP1, IDH1, IDH2, and ETV6. While some are more common than others, no single gene has been reported in more than approximately one-third of cases. Most of these are useful as adjunctive diagnostic markers for clinically/microscopically ambiguous cases, to help establish a more firm diagnosis and, potentially, as markers of clonal disease that can be used to monitor for disease progression and response to interventions.

The spectrum of genetic abnormalities that are relevant in MDS is broad, and includes specific sequence variants within a large number of genes as well as a wide range of aberrations in other genes. While it is possible to assess the former of these with single gene assays, it is functionally impractical given the number of hotspot variants and number of genes. The latter require more complete coverage of the entire gene. In this regard, MDS is an appropriate indication for multiplexed sequencing, which is typically performed by next generation sequencing.

The following molecular genetic biomarkers are considered necessary for diagnosis and management of select MDS: TP53, EZH2, ETV6, ASXL1, RUNX1, SF3B1. These variants represent essential determinants of prognosis and therapy and are shown to lead to safe and effective therapy selection.

Myeloproliferative Neoplasms (MPN)

MPNs can be subdivided in two main categories based upon the presence or absence of BCR-ABL1: chronic myeloid leukemia (CML) and non-CML MPNs. The main non-CML MPNs, also termed classical MPNs, including essential thrombocythemia (ET), primary myelofibrosis (PMF), and polycythemia vera (PV), had traditionally been defined by laboratory criteria such as thrombocytosis, marrow fibrosis, and erythrocytosis, respectively. Non-CML MPN treatment can range from observation to targeted therapies to hematopoietic stem cell transplantation (HCT), with the principal determining factors being the patient's overall health and co-morbidities, presence of fibrosis or increased blasts, molecular and prognostic categorization. Other less common diagnostic entities within the non-CML MPNs include chronic neutrophilic leukemia (CNL)and chronic eosinophilic leukemia (CEL).

While the definitions of the entities within MPN are fairly distinct, in practice, phenotypic overlap is common, and definitive classification can be challenging based solely on clinical grounds and traditional laboratory tests, such as complete blood count (CBC) and bone marrow biopsy. At diagnosis, the discrimination from reactive conditions is often critical, and the demonstration of several specific clonal molecular alterations in clinically or morphologically ambiguous cases can expedite an MPN diagnosis before progression to a more overt, life-threatening, condition. Accordingly, one or more MPN-restricted, driver mutations are included in practice guideline recommendations as necessary for the diagnosis or management of patients with MPN or MPN-like conditions, including Janus kinase 2 (JAK2), calreticulin (CALR), and myeloproliferative leukemia virus (MPL). Driver mutations are usually mutually exclusive.

The following molecular genetic biomarkers are considered necessary for diagnosis and management of select MPNs: JAK2, CALR, MPL, Triple Negative, ASXL1, EZH2, IDH1/2, SRSF2, TP53. These variants represent essential determinants of prognosis and therapy and are shown to lead to safe and effective therapy selection.

CODING

The following CPT codes may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

RELATED POLICIES
Genetic Testing Services

PUBLISHED
Provider Update, June 2023

REFERENCES

1. Centers for Medicare and Medicaid Services. Local Coverage Determination (LCD): Genomic Sequence Analysis in the Treatment of Hematolymphoid Diseases (L37606)
2. Centers for Medicare and Medicaid Services. Local Coverage Article: Billing and Coding: Genomic Sequence Analysis in the Treatment of Hematolymphoid Diseases (A56793)